Remarks

Claims 35-54 and 69 are pending in this application. Claims 35 and 69 are amended herein. Claim 35 is amended to clarify the specific structure of the Kozak (ribosomal binding) sequence in the flavivirus transcription unit. Claim 69 is amended to recite additional structural characteristics of the ribosomal binding sequence.

Support for the amendments to the claims is found, for instance in Figures 2, 6 and 7, which clearly reflect a particular location and sequence of the ribosomal binding sequence in each of the constructs. Additional support for this language is also found in Example 1, at page 19, lines 12-13.

Claims 35-54 and 69 are not obvious in view of Phillpotts and Kozak (1987).

Claims 35-54 and 69 were rejected under 35 U.S.C. §103(a) as obvious in view of Phillpotts *et al.* (1996) combined with Kozak (1987). The Office action alleges that Phillpotts discloses isolated nucleic acids that include a transcriptional unit expressing a flavivirus immunogen, specifically St. Louis Encephalitis (SLE) Virus prM/E. The Office action admits that Phillpotts does not disclose any Kozak sequence but contends that simply because "Kozak compared the translation initiation sequences of several hundred higher eukaryotes and ascertained the optimal sequences for translational initiation," it would have been obvious to one having ordinary skill in the art "to include a Kozak translational consensus sequence in the transcriptional unit of Phillpotts..." The Office action also contends that Konishi *et al.* (1992) supports these allegations and demonstrates that expression of a construct containing such a transcription unit results in production of immunogenic subviral particles. Applicant traverses.

At least three basic requirements must be met to establish a *prima facie* case of obviousness. First, the Office must show how the prior art references teach all of the limitations of the claims. M.P.E.P. § 2143.03. Second, the Office must establish that there was a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, the Office must demonstrate that there was a reasonable expectation of success for achieving the invention in the prior art. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must both be found in the prior art and not based on an Applicant's disclosure. M.P.E.P. § 2142.

The prior art did not teach the limitations of the subject claims

The claims as amended are directed to specific constructs for expressing an immunogenic flavivirus antigen in a host cell, which are described in Applicant's specification. The claimed constructs include a transcriptional unit comprising (1) a signal sequence consisting of a prM signal peptide sequence, and (2) a ribosomal binding sequence comprising the sequence GCCGCCGCC located at positions -9 through -1 relative to a start codon. The constructs are capable of expressing an immunogenic flavivirus antigen after introduction into host cells. It would not have been obvious, based on the cited references, to devise a construct including all of the features of the amended claims. None of the references individually or in any combination would have led the ordinarily skilled artisan to generate "a transcriptional unit" comprising "a signal sequence consisting of a prM signal peptide sequence and a ribosomal binding sequence comprising GCCGCCGCC located at position -9 to -1 relative to a start codon."

Phillpotts discloses a nucleic acid construct that includes a transcriptional unit that encodes the prM/E proteins of St. Louis encephalitis virus (SLE). Thus, Phillpotts can reasonably be interpreted as disclosing a transcriptional unit that comprises (1) a signal sequence consisting of a prM signal peptide sequence. As admitted in the Office action, there is no mention in Phillpotts of a ribosomal binding site. Thus, Phillpotts cannot be interpreted as disclosing a transcription unit with (2) a ribosomal binding sequence comprising the sequence GCCGCCGCC located at positions -9 to -1 relative to a start codon.

Konishi (1992) is cited as demonstrating that expression of a nucleic acid construct encoding a flavivirus prM/E antigen results in the production of immunogenic subviral particles. Konishi discloses recombinant vaccinia virus vectors that encode Japanese encephalitis virus prM/E proteins. The synthetic vaccinia virus "H6 promoter immediately preceded the ATG start codon" of the prM/E open reading frame (*see*, construction details, Konishi *et al.*, *Virology* 185:401-410, 1991, also of record). Thus, the constructs disclosed by Konishi did not include a Kozak sequence immediately upstream of the start codon.

Kozak (1987) discloses the results of a mutagenesis study of the nucleotides flanking a consensus ribosomal binding site operably linked to a preproinsulin gene. Nothing in this

reference relates to a transcription unit that includes a viral antigen, and nothing in this reference relates to expressing such a viral antigen in a host cell. Thus Kozak does not provide any teaching of inserting a ribosomal binding sequence comprising the sequence GCCTCCTCC located at positions -9 to -1 to a viral antigen (such as an immunogenic flavivirus antigen) for the purpose of synthesizing a viral antigen in a cell.

Thus, the cited references cannot reasonably be interpreted as providing all of the limitations of the claims.

The cited references do not provide a motivation to combine the teachings of Phillpotts and Kozak

Even if Phillpott and Kozak are interpreted as supplying all of the limitations of the claimed invention, neither of these references (nor Konishi, nor any other reference of record) provides any motivation for inserting a Kozak translation initiation sequence into the construct of Phillpotts. The Office action indicates that because "Kozak compared the translation initiation sequences of several hundred higher eukaryotes and ascertained the optimal sequences for translational initiation," it would have been obvious to one having ordinary skill in the art "to include a Kozak translational consensus sequence in the transcriptional unit of Phillpotts..." Again, Applicant disagrees.

As discussed above, Kozak simply does not relate to expression of viral antigens for the production of nucleic acid vaccines. To select this reference for the rejection requires reliance on the teachings of Applicant's specification. Phillpotts states that mice injected with an SLE prM/E protein under the control of the cytomegalovirus immediate early protein promoter were protected against lethal challenge with virulent virus (abstract, lines 4-8). Based on Phillpotts, one of skill in the art would conclude that adequate protection could be obtained using a CMV promoter, despite the relatively poor survival rate of the injected mice. There would be no motivation to modify Phillpotts construct.

More importantly, despite the fact that the cited Kozak reference was published nine years prior to the cited Phillpotts reference, Phillpotts made no attempt to introduce a ribosomal

binding (Kozak) sequence. Similarly, Konishi (published five years following the publication of the cited Kozak reference) elected not to incorporate a Kozak consensus sequence, choosing instead to rely on the H6 promoter sequence to regulate expression. Thus, although skilled practitioners, such as Phillpotts and Konishi (and their colleagues) set out to produce vaccines against flaviviruses, they failed to appreciate the value of inserting a Kozak sequence into their constructs to increase expression of the flavivirus antigen. Nothing in the cited references addresses or remedies this failure in their experimental approach.

Thus, none of the cited references supplies a motivation to combine the teachings of Phillpotts and Kozak to obtain the claimed constructs.

The cited references do not provide a reasonable expectation of success

Furthermore, nothing in Phillpotts, Kozak or Konishi provides any indication whatsoever that adding a ribosomal binding at a position adjacent to the start codon would increase expression of the flavivirus antigen. Despite the fact that both Phillpotts and Konishi were published well after the publication of Kozak, nothing in any of these references provides a reasonable expectation that adding a ribosomal binding site to a nucleic acid vaccine construct would improve expression (and therefore antigenicity) of the construct. It was not until Applicant recognized the value of introducing a ribosomal binding site with the sequence GCCGCCGCC at positions -9 to -1 with respect to the start codon that the benefits of the claimed invention could be realized.

Accordingly, it appears that the Office is impermissibly using Applicant's own disclosure to supply both the motivation to combine the nucleic acid vaccine constructs of Phillpotts with the ribosomal binding consensus sequence of Kozak, and the expectation that such a combination would lead to success. Such hindsight analysis is expressly prohibited by MPEP §2142. Given the lack of any teaching in the cited references that would motivate a skilled practitioner to insert a ribosomal binding site into a nucleic acid flavivirus vaccine construct, or provide any reasonable expectation that such an insertion would provide a beneficial effect in increasing antigenicity, the Office has not, and cannot, make an obviousness rejection on the basis of the cited references.

In view of the foregoing, Applicant respectfully submits that the Office has not made a proper *prima facie* case of obviousness, and the rejection should be withdrawn.

The claimed constructs provide unexpectedly superior results

Even assuming, for the sake of argument, that the Office has made a proper *prima facie* case of obviousness, Applicant traverses on the grounds that the claimed constructs provide an unexpectedly superior result as compared to the prior art.

For example, no prior art reference of record in this application, or known to the Applicant, discloses a nucleic acid construct that yields the large quantities of subviral particles produced from Applicant's constructs. More importantly, the claimed constructs elicit a high titer of neutralizing antibodies after only a single injection. None of the constructs described in the cited references are capable of eliciting substantial titers of neutralizing antibodies against flavivirus M or E proteins. Indeed, Phillpotts states that "[n]o virus neutralizing activity was detected...despite the presence of antibody to gE..." following immunization with an SLE prM/E construct. Konishi discloses that neutralizing antibodies were obtained only when large quantities of purified particles were injected with adjuvant or when a high titer of infectious recombinant vaccinia virus was used as a vaccine. In contrast, as shown in Table 3 of the subject specification, after receiving a single injection with the claimed flavivirus nucleic acids, mice exhibited substantial neutralizing antibody titers that increased up to 1:160 by nine weeks after immunization. Immunized animals continued to be antibody-positive for more than one year. Furthermore, the claimed nucleic acid vaccines are capable of producing an antibody response in mice as young as 3 days of age, and produce a maternal antibody titer high enough to provide passive immunity to suckling pups.

Thus, the claimed flavivirus nucleic acids possess advantageous properties with respect to vaccination against flaviviruses that are not described in any of the cited references. These properties are conferred by the particular features enumerated in the claims, including the use of the sequence GCCGCCGCC located at position -9 to -1 with respect to the ATG start site in combination with a signal sequence consisting of a prM signal peptide sequence. Accordingly, claims 35-54 and 69 are not rendered obvious by the cited references, and the rejection should be withdrawn.

Conclusion

Applicant submits that the claims 35-54 and 69 are now in condition for allowance. Therefore, a Notice of Allowance at an early date is respectfully requested. If any other issues of patentability exist, the Examiner is requested to telephone the undersigned prior to the preparation of any additional written action.

Respectfully submitted,

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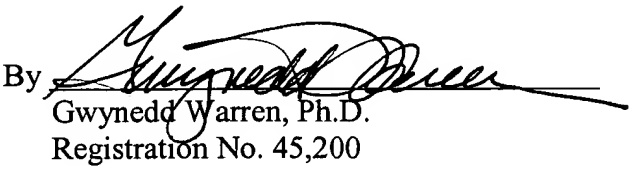
By 
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